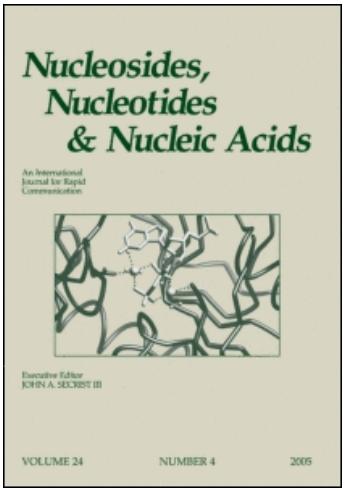

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The Synthesis of [(β-D-Ribofuranosyloxy)-methyl]nucleosides

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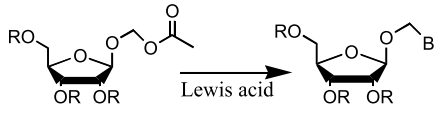
ABSTRACT

The coupling reaction of acetoxymethoxy ribofuranoside **4** with nucleic acid bases **5a–f** to synthesize novel (ribofuranosyloxy)methyl uracil, thymine, cytosine, adenine, guanine derivatives **6a–g** respectively in preference to the expected formation of natural nucleosides 2′,3′,5′-tri-O-benzoyl uridine, methyluridine, cytidine, adenosine and guanosine **7a–g** is described. Detailed study of these reactions catalysed by Lewis acids TMSOTf and $SnCl_4$ is described. TMSOTf exhibited selectivity for the formation of ribofuranosyloxy methyl derivatives **6a–g** rather than **7a–g**. Reason for formation of **6a–g** is explained by HSAB principle.



R=Bz

B=uracil,thymine,cytosine
adenine,guanine

Key Words: Acetoxymethoxy; Methyluridine; Cytidine; Adenosine; Guanosine.

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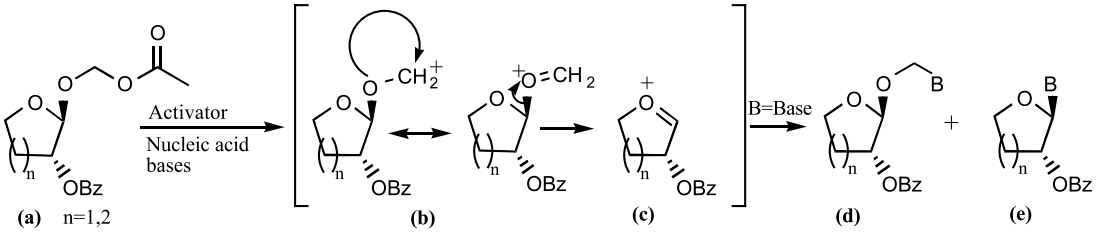
INTRODUCTION

The Vorbruggen[1–7] modification of Hilbert–Johnson reaction[8] of persilylated heterocyclic bases with peracylated sugars in presence of Friedel–Crafts catalysts has become a standard synthetic method for preparation of natural nucleosides routinely in high yields. The reaction of silylated pyrimidines and purines with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranoside is known to proceed via a stable electrophilic 1,2-α-acyloxonium intermediate.[9–13] The various mechanisms of all these synthetic methods of nucleoside synthesis have been earlier studied, carefully reviewed[14,15] and discussed.[16]

In this report we describe our experiments aimed at the concept of fine-tuning the acetoxymethoxyglycosyl derivative **a** to generate glycosyloxy carbocation **b** and capture it by nucleic acid bases **B** to achieve synthesis of novel glycosyloxymethyl nucleosides **d** (Scheme 1). Glycosyloxy carbocation **b** has a tendency to fragment further to the thermodynamically more stable 'glycosyl cation **c**' and form the natural nucleoside **e** when captured by **B**. The results of this fundamentally new approach might have some significance in developing newer themes in carbohydrate chemistry.[17–20]

The key acetoxymethoxy substrate **a** required to illustrate the above concept was elegantly synthesized from 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-α/β-D-ribofuranoside **(1)**[21,22] by initial reaction with propargyl alcohol, $BF_3.Et_2O$ in $CHCl_3$ at room temperature to isolate propynyl ribofuranoside derivative **2**[23] (Scheme 2). Compound **2** on further reaction with a catalytic amount of Hg $(OCOCF_3)_2$ in acetone-H_2O (2:1) at room temperature gave the corresponding keto derivative **3**. Baeyer–Villiger oxidation of keto compound **3** with m-CPBA in $CHCl_3$ gave 1-[(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyloxy)methyl]acetate (**4**) as a crystalline solid, mp 71°C in 42% overall yield starting from **1**.[24] Compound **4** was characterized by ^{1}H NMR (the methylene protons at δ 5.36, δ 5.42 as an AB type quartet, J = 7.5 Hz and H-1 at δ 5.56 as a singlet) and ^{13}C NMR (the methylene carbon at δ 84.7 and C-1 at δ 103.9).

In order to study the potential of the envisaged concept a Vorbruggen modified Hilbert–Johnson reaction of **4** with *bis*(trimethylsilyl) uracil (**5a**), *bis*(trimethysilyl)-thymine (**5b**) and *bis*(trimethylsilyl) cytosine **(5c)**[25] was affected (Scheme 3) with the Friedel–Crafts catalyst Sn(IV)Cl/$CHCl_3$ at room temperature for 4–6 h. It resulted in the formation of a mixture of ribofuranosyloxymethyl uracil **6a**, -thymine **6b**, -cytosine **6c** derivatives (24–30% yield) along with the corresponding natural nucleosides



Scheme 1. Mechanism proposed for the formation of [(β-D-ribofuranosyloxy)methyl]nucleosides.

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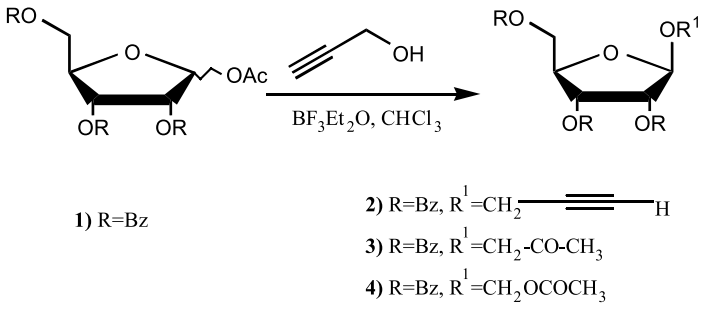

Scheme 2. Synthesis of acetoxymethoxy ribofuranoside **4.**

2′,3′,5′-tri-O-benzoyluridine, 5-methyluridine, and cytidine (**7a–c** respectively, 45–47% yield) (Table 1, entries i,iii,v).

The mixture of ribofuranosyl derivatives **6a–c** and **7a–c** was separated by column chromatography and characterized by ^{1}H NMR spectra as 1-[2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyloxy)methyl]uracil (**6a**), 1-[(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyloxy) methyl]thymine (**6b**), 1-[(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyloxy)methyl]cytosine (**6c**) respectively (the methylene protons at δ 5.10–5.15 (1 H) and δ 5.36–5.40 (1 H) as an AB type quartet, J = 10 Hz and H-1′ at δ 5.50–5.60 as a singlet) and ^{13}C NMR (the methylene carbon at δ 78.0–80.0 and C-1 at δ 104.2–104.7). Unambiguous assignment of structure for **6a–c** was accomplished after hydrolysis ($NaHCO_3$/MeOH) to isolate **8a–c** respectively, characterized (Scheme 3) as 1-[(-β-D-ribofuranosyloxy)-methyl]uracil (**8a**), 1-[(-β-D-ribofuranosyloxy)methyl]thymine (**8b**) and 1-[(-β-D-ribofuranosyloxy)methyl]cytosine (**8c**) respectively by ^{1}H NMR (the methylene protons at δ 5.20–5.27 (1 H) and δ 5.35–5.40 (1 H) as an AB type quartet J = 10 Hz and H-1′ at δ 5.20–5.22 as a singlet) and ^{13}C NMR (the methylene carbon at δ 82.5–83.5 and C-1′ at δ 105.2–106.0).

The differentiation of N-1 alkylation from N-3 of **8a–c** was readily accomplished by comparison of ultraviolet spectra of the compounds in neutral vs 0.1 N alkali.[26–28] They were characterized as N-1alkylation products as they showed less than a 2-mμ shift. Natural nucleosides **7a–c** were characterized as 2′,3′,5′-tri-*O*-benzoyluridine (**7a**), 5-methyluridine (**7b**) and cytidine (**7c**) respectively (Scheme 3) by comparison of their ^{1}H NMR spectral data and melting point with those reported in literature.[29] Formation of compounds **6a–c** and **7a–c** can be explained from the capture of oxymethyl carbocation **b** and ribofuranosyl cation **c** respectively by the base **B (a–c)** (Scheme 1). In order to drive the reaction towards the formation of **6** alone, we have studied the replacement of $SnCl_4$ by the weaker Friedel–Crafts catalyst $(CH_3)_3SiOSO_3CF_3$ (TMSOTf) to perform the coupling reaction.[30] Thus, reaction of **4** with **5a** (entry ii) and **5b** (entry iv) was carried out with TMSOTf/$CHCl_3$ at reflux temperature (3–5 h) to isolate **6a** and **6b** respectively in high yield, and formation of **7a** and **7b** was not observed (Table 1). The generality of the reaction was studied for coupling of **4** with cytosine derivative **5c** under similar reaction conditions, resulting in the isolation of **6c** and **7c** in a ratio of 1:1 respectively (Table 1, entry vi) indicating moderate selectivity,

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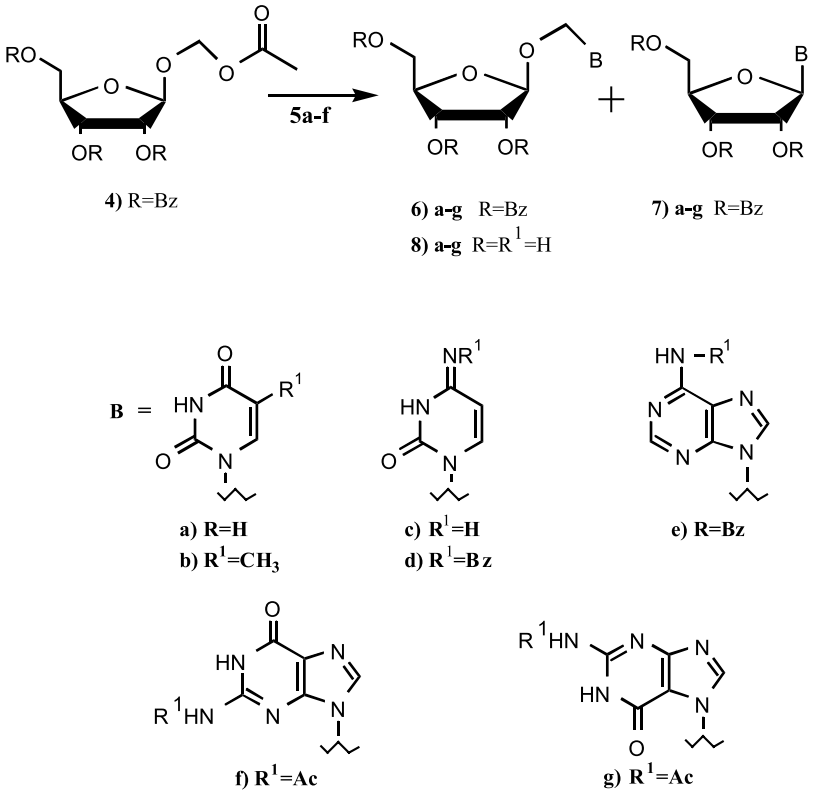

Scheme 3. Synthesis of [(β-D-ribofuranosyloxy)methyl]nucleosides.

probably due to the higher basicity of cytosine.[31,32] In order to achieve the selective formation of **6c**, coupling of **4** with *bis*(trimethylsilyl)-N^4-benzoylcytosine (**5d**)[33] was attempted, resulting in the isolation of N^4-benzoyl-1-[(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyloxy)methyl]cytosine (**6d**) and N^4-2,3,5-tetra-*O*-benzoyl cytidine (**7d**) in a ratio of 3:1 respectively (entry vii). Thus, use of the N^4-benzoyl derivative of cytosine in the coupling reaction has resulted in the isolation of the desired product **6d** in higher yield. In order to establish the generality of the reaction, coupling of **1** with bis(trimethylsilyl)-N^6-benzoyladenine (**5e**)[34] was carried out in $SnCl_4$/MeCN at room temperature to isolate **6e** and **7e** respectively, in a ratio of 1:2 (entry viii) (Scheme 3). A similar observation was made in the coupling of **4** with **5a–c**. Compound **6e** was characterized analogously to **6a–c**. In order to assign the regiochemistry, **6e** was hydrolyzed ($NaHCO_3$/methanol) to 9-[(-β-D-ribofuranosyloxy)methyl]adenine (**8e**) and characterized by an ^{1}H NMR spectrum analogous to natural nucleosides from the appearance of H-2 and H-8 protons at δ 8.25 and δ 8.20, respectively, indicating it to be the N^9 isomer.[35] Natural nucleoside **7e** was characterized as N^6,2,3,5-tetra-*O*-benzoyladenosine (**7e**) by comparison of its ^{1}H NMR spectrum, melting point and optical rotation with that reported in literature[29] and was found to be the N^9 regioisomer. In order to enhance the formation of **6e**, coupling of **4** with **5e** was studied

Table 1. Coupling of **4** with nucleic acid bases **5a–f**.

Entry	Solvent	Temperature	Catalyst	Reaction time (h)	**6a–f, 5ff** (% yield)	**7a–f, 6ff**	Ratio of **6/7** (%yield)
i	a	RT	A	5	6a (30.6)	7a (46)	1.0:1.5
ii	a	reflux	B	3	6a (98.1)	7a (0)	1.0:0.0
iii	a	RT	A	4	6b (28.0)	7b (45.2)	1.0:1.6
iv	a	reflux	B	4	6b (78.5)	7b (0)	1.0:0.0
v	a	RT	A	6	6c (29.5)	7c (47.3)	1.0:1.6
vi	a	reflux	B	6	6c (36.5)	7c (36.5)	1.0:1.0
vii	a	reflux	B	4	6d (52.0)	7d (17.0)	3.0:1.0
viii	b	RT	A	16	6e (20.6)	7e (39.6)	1.0:1.9
ix	b	RT	B	16	6e (45.4)	7e (34.9)	1.3:1.0
x	b	reflux	B	2	6e (30.2)	7e (32.0)	1.0:1.0
xi	a	RT	B	16	no reaction	–	–
xii	a	reflux	B	2	decomposition	–	–
xiii	b	RT	A	18	6f:6g (17.4) N^9:N^7 = 1:12.2	7f:7g (27.8) N^9:N^7 = 1:7.2	1.0:1.6
xiv	b	reflux	A	1	6f:6g (10.2) N^9:N^7 = 1:2.4	7f:7g (79.6) N^9:N^7 = 1.7:1.0	1.0:7.8
xv	b	RT	B	17	6f:6g (22.7) N^9:N^7 = 1.1:1.0	7f:7g (61.3) N^9:N^7 = 1.0:1.6	1.0:2.7
xvi	b	reflux	B	3	6f:6g (21.3) N^9:N^7 = 1.2:1.0	7f:7g (38.3) N^9:N^7 = 1.4:1.0	1.0:1.8
xvii	c	reflux	B	2	6f:6g (57.0) N^9:N^7 = 1.1:1.0	7f (0)	1.0:0

a = $CHCl_3$; b = CH_3CN; c = 1,2-Dichloroethane; A = Sn(IV)Cl; B = TMSOTf.

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by use of a weaker catalyst (TMSOTf) in solvents such as $CHCl_3$ (entry xi, xii) and MeCN (entry ix, x) at room temperature to reflux temperature. The best result was the formation of a mixture of **6e** and **7e** respectively (Table 1), in a ratio 1.3:1 in MeCN at room temperature (entry ix). The observed moderate selectivity in this reaction needs to be studied in detail. The scope and utility of the coupling reaction was also examined for the preparation of ribofuranosyloxymethyl guanine derivatives in view of their importance as pharmacologically active compounds such as acyclovir,[36,37] ganciclovir[38,39] and penciclovir.[40] Coupling of **4** and N^2-acetyl-*tris*(trimethylsilyl)-guanine (**5f**)[41] in $SnCl_4$/MeCN at room temperature gave **6f**,**6g**:**7f**,**7g** (a ratio of 1:1.6, entry xiii) while at reflux temperature coupling resulted in the formation of the undesired nucleosides in larger amount (a ratio of 1:7.8, entry xiv). Reactions by change of solvent and catalyst was attempted to enhance the selective formation of **6f**,**6g**. Thus, coupling of **4** with **5f** in TMSOTf/MeCN at room temperature gave **6f**,**6g**:**7f**,**7g** in a ratio of 1:2.7 (entry xv), and at reflux temperature it changed to 1:1.8 (entry xvi). The change of solvent to 1,2-dichloroethane and reaction at reflux temperature has exhibited the desired selectivity and resulted in the formation of **6f**,**6g** in 57% isolated yield (entry xvii), while formation of **7f**,**7g** was not observed. TMSOTf was found to be the suitable catalyst for preparation of ribofuranosyloxymethyl derivatives **6a–g**. Compounds **6f**,**6g** and **7f,7g** were found to be a mixture of N^9/N^7 regiosiomers, **6f**,**6g** were characterized analogously to **6a–c**. In order to assign the regiochemistry[42–44] **6f**,**6g** were hydrolyzed to **8f**,**8g** respectively (Scheme 3) and unambiguously characterized[42–44] by the ^1H and ^{13}C NMR as 9-[(-β-D-ribofuranosyloxy)methyl] guanine (**8f**) (the H-8 at δ 7.75 as a singlet, NH_2 at δ 6.55; C-5 at δ 116.4, C-8 at δ 137.7 and C-4 at δ 151.2) and 7-[(-β-D-ribofuranosyloxy)methyl]guanine (**8g**) (the H-8 at δ 8.0 as singlet, NH_2 at δ 6.20; C-5 at δ 105.7, C-8 at δ 145.0 and C-4 at δ 161.0) respectively.[42–44] N^2-Acetyl-9-(2,3,5-tri-*O*-benzoy-β-D-ribofuranosyl)guanine (**7f**) and N^2-acetyl-7-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl) guanine **(7g)** were characterized as N^9 and N^7 linked natural nucleosides respectively by comparison of their ^1H NMR spectra and melting point with that reported in literature.[29,42–44]

Formation of regiosiomers N^9 (**6f** and **7f**) and N^7 (**6g** and **7g**) was studied by change of solvent (MeCN,1,2-dichloroethane), temperature (room temperature, reflux) and catalyst (Sn(IV)Cl, TMSOTf). From these experiments it was observed that in the formation of regioisomers **6f**,**6g** and **7f**,**7g** respectively, the N^7 isomer predominated over N^9 in $SnCl_4$ under kinetically controlled conditions, where as under thermodynamic conditions no such selectivity was observed in $SnCl_4$ or TMSOTf. The lack of regioselectivity observed in the present study is ascrobed to the difference in reactivity of donors **4** and **1**, bearing the acetoxymethoxy and the acetyl leaving group respectively. Attempted isomerisation[35,45] of N^7 isomer **6g** in TMSOTf/MeCN at reflux temperature resulted in the decomposition, and formation of **6f** (N^9 isomer) or natural nucleosides **7f** and **7g** was not observed.

We have earlier reported[24] that acetoxymethoxy glycopyranosides **a** couple with alcohols (sugar and simple alcohols) to form *O*-glycosides due to the capture of glycosyl cation **c**, while formation of products resulting from the capture of glycosyloxymethyl carbocation **b** was not observed. In the present study we have shown that coupling with nitrogen bases lead to the formation of products by capture of intermediate **b** in preference to **c**. The reason for selectivity appears to be according to the HSAB principle.[46–48] The glycosyl cation **c** is a hard acid and couples with hard

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bases[31,32,49] (alcohols, cytosine and adenine), where as carbocation **b** is a borderline soft acid and is captured by soft base[31,32,49] (uracil, thymine and guanine).

In summary synthesis of novel ribofuranosyloxymethyl uracil, thymine, cytosine, adenine and guanine was achieved by fine tuning of the acetoxymethoxy leaving group of ribofuranoside. Application of this method for the synthesis of other glycosyl derivatives is under investigation.

EXPERIMENTAL

^{1}H NMR spectra were recorded using the following instruments: at 200 MHz on a Varian Gemini, at 300 MHz on a Bruker Avance; at 400 MHz on a Varian Unity; at 500 MHz on a Varian Inova, with tetramethyl silane as internal standard for solutions in deuteriochloroform. *J* values are given Hz. ^{13}C NMR spectra were taken with Varian Gemini (50 MHz), Bruker Avance (75 MHz) spectrometer with $CDCl_3$ as internal standard (C 77.0) for solutions in deuteriochloroform, DMSO-d_6 (C 39.7) for solutions in deuterio dimethyl sulfoxide, dioxane (C 67.3) for solutions in deuterated water. Optical rotations were measured with a JASCO DIP-370 instrument. Melting points were determined by using Fischer–John's melting point apparatus and are uncorrected. IR spectra were taken with a Perkin–Elmer 1310 spectrometer. UV spectra were recorded on a Shimadzu UV 160A spectrometer. Organic solutions were dried over anhydrous Na_2SO_4.

A Typical Procedure for Coupling of Ribofuranoside Derivative 4 with Nucleic Acid Bases 5a–f (Method A: $SnCl_4$ or Method B: Trimethylsilyltrifluoromethane sulfonate (TMSOTf) (1.2–2.0 mmol, 0.5N in $CHCl_3$ or MeCN or 1,2-dichloroethane). To a solution (20 ml) of ribofuranoside derivative **4** (1.0 mmol) and silylated nucleic acid bases **5a–f** (1.2 mmol) at 0°C was added the catalyst under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 4–18 h or reflux temperature for 1–6 h, progress of the reaction was monitored by TLC. After completion of the reaction it was neutralized with saturated aqueous $NaHCO_3$ solution and filtered through a celite pad. The filtrate was extracted into $CHCl_3$ (30 ml), organic phase was separated, washed with brine, dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure to obtain a residue. The residue was separated by column chromatography [SiO_2, 60–120 mesh, ethyl acetate:chloroform] to isolate the title compounds **6a–g** and **7a–g**.

2-Propynyl 2,3,5-Tri-*O*-benzoyl-β-D-ribofuranoside (2). To a solution of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-α/β-D-ribofuranoside (**1**) (20.0g, 39.7 mmol) in dry $CHCl_3$ (200 mL) was added propargyl alcohol (2.8 mL, 47.6 mmol) and $BF_3.Et_2O$ (6 mL, 47.6 mmol) at 0°C. The reaction mixture was stirred at room temperature for 5 h. After completion of the reaction, anhydrous K_2CO_3 (6.0 g) was added, stirred for further 30 min., filtered, and the residue was washed with $CHCl_3$ (50 mL). The filtrate was transferred to a separating funnel, washed with water (100 mL × 2) and brine (100 mL). The organic phase was separated, dried (Na_2SO_4) and concentrated to obtain a residue. The residue was chromatographed [SiO_2; hexane–ethyl acetate (9:1)] to isolate the *title compound* **2** (13.3 g,

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68%) as a crystalline solid. mp 56°C; $[\alpha]_D$ 12.4 (c 1.0, $CHCl_3$); IR (KBr) ν_{max} 3277, 3238, 2954, 2884, 2108, 1731, 1717, 1604, 1485, 1392, 1261, 1170, 1123, 1093, 1031 and 954 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$) δ 2.41 (1H, t, C≡CH), 4.25, 4.35 (2H, AB quartet, J = 9.3 Hz, CH_2–C≡C), 4.52 (1H, dd, J = 13.0, 6.0 Hz, H5), 4.60–4.80 (2H, m, 4H, H5′), 5.48 (1H, s, H1), 5.72 (1H d, J = 4.6 Hz, H2), 5.90 (1H dd, J = 3.7 Hz, H3), 7.25–8.25 (15H, m, aromatic); ^{13}C NMR (50 MHz; $CDCl_3$) δ 54.5 (H*C*≡C–), 64.5 (C5), 72.1 (C4), 75.7 (C3), 75.9 (O–*C*H_2–C), 78.3 (HC≡*C*–), 79.4 (C2), 103.4 (C1), 128–135 (aromatic), 165.03, 165.77 and 166.06 (C=O,ester); FAB-MS m/z: 523 [M^+ + Na]; Anal.Calcd for $C_{29}H_{24}O_8$: C,69.59; H, 4.83. Found: C, 69.42; H, 4.78.

2-(Oxopropoxy) 2,3,5-Tri-*O*-benzoyl-β-D-ribofuranoside (3). To a solution of 2-propynyl 2,3,5-tri-*O*-benzoyl-β-D-ribofuranoside (**2**) (13.0 g, 26 mmol) in acetone: H_2O (200 mL, 2:1) was added $Hg(OCOCF_3)_2$ (2.21 g, 5.18 mmol). The reaction mixture was stirred at room temperature for 6h. After completion of the reaction, acetone was evaporated, the resulting residue was dissolved in ethyl acetate (200 mL), washed with 10% aqueous KI solution (100 mL × 2), 20% aqueous hypo solution (100 mL × 2) and brine (100 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated to obtain the *title compound* **3** (12.9 g, 96%) as a solid. mp 75°C; $[\alpha]_D$ 3.1 (c 1.0, $CHCl_3$); IR (KBr) ν_{max} 2977, 2953, 2885, 2870, 2830, 1731, 1715, 1584, 1446, 1308, 1262, 1108, 1046, 1015 and 708 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$) δ 2.10 (3H, s, CH_3), 4.10, 4.24 (2H, AB type quartet, J = 10.0 Hz, OCH_2C), 4.52 (1H, dd, J = 13.0, 6.0 Hz, H5), 4.60–4.80 (2H, m, H4,H5′), 5.30 (1H, s, H1), 5.80 (1H, d, J = 4.7 Hz, H2), 5.90 (1H, dd, J = 3.7 Hz, H3), 7.20–8.25 (15H, m, aromatic); ^{13}C NMR (50 MHz; $CDCl_3$) δ 26.3 (CH_3), 64.3 (C5), 71.9 (C4), 72.3 (O*C*H_2C), 75.3 (C3), 79.5 (C2), 105.1(C1), 125–135 (aromatic), 165.0, 165.2 and 165.1; (C=O,ester); FAB-MS m/z: 541 [M^+ + Na]; Anal. calcd for $C_{29}H_{26}O_9$:C, 67.17; H, 5.05. Found: C, 67.37; H, 5.18.

1-[(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyloxy)methyl]acetate (4). To a solution of 2-(oxopropoxy)2,3,5-tri-*O*-benzoyl-β-D-ribofuranoside (**3**) (12.0g, 23.2 mmol) in dry $CHCl_3$ (120 mL) was added m-CPBA (9.6 g, 55.6 mmol). The reaction mixture was stirred at room temperature for 12h. After completion of the reaction, the reaction mixture was diluted with $CHCl_3$ (150 mL), washed with saturated aqueous $NaHCO_3$ solution (150 mL × 3, water (150 mL), brine (150 mL) and dried (Na_2SO_4). The solvent was concentrated to give a residue which was purified by silica gel chromatogrpahy (SiO_2, hexane:ethyl acetate, 9:1) to obtain the *title compound* **4** as a white solid. mp 71°C; $[\alpha]_D$ 8.0 (c 1.0, $CHCl_3$); UV λ_{max} (MeOH) nm: 274; IR (KBr) ν_{max} 3062, 3015, 2938, 1752, 1731, 1604, 1430, 1261, 1107, 1046, 1015 and 708 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$) δ 2.10 (3H, s, CH_3), 4.54 (1H, dd, J = 13.0, 4.65 Hz, H5), 4.66–4.86 (2H, m, H4,H5′), 5.36, 5.42 (2H, AB type quartet, J = 7.5 Hz, OCH_2O), 5.56 (1H, s, H1), 5.75 (1H, d, J = 6.5 Hz, H2), 5.90 (1H, dd, J = 4.4 Hz, H3), 7.20–8.20 (15H, m, aromatic); ^{13}C NMR (50 MHz; $CDCl_3$) δ 20.8 (CH_3) 64.4 (C5), 71.9 (C4), 75.4 (C3), 79.5 (C2), 84.7 (O*C*H_2O), 103.9 (C1), 125–135 (aromatic), 165.0, 165.2 and 170.1 (C=O, ester); FAB-MS m/z: 535 [M^+ + H]; Anal. calcd for $C_{29}H_{26}O_{10}$:C, 65.16; H, 4.90. Found: C, 65.27; H, 5.11.

1-[(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyloxy)methyl]uracil (6a). Prepared according to method B (2.24 mmol) by reacting **4** (1.0 g, 1.87 mmol) and **5a** (0.57 g,

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2.24 mmol) in $CHCl_3$ (40 mL) at reflux for 3 h to isoltate the title compound as a pale yellow solid (1.07 g, 98.1% yield). mp 78–80°C; $[\alpha]_D$ 16.0 (c 1.0, $CHCl_3$); UV λ_{max} (MeCN) nm: 259; IR (KBr) ν_{max} 3062, 2107, 1723, 1677, 1446, 1262, 1154, 1086, 1015, 816 and 692 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$) δ 4.60 (1H, dd, *J* = 13.0, 5.5 Hz, H5′), 4.60–4.80 (2H, m, H4′,H5″), 5.14, 5.38 (2H, AB type quartet, *J* = 10.0 Hz, OCH_2N), 5.50 (1H, s, H1′), 5.62 (1H, d, *J* = 5.6 Hz, H2′), 5.65 (1H, d, *J* = 5.5 Hz, H5), 5.82 (1H, dd, *J* = 4.0 Hz, H3′), 7.18 (1H, d, H6), 7.20–8.20 (15H, m, aromatic), 9.0 (1H, br s, NH); ^{13}C NMR (50 MHz; $CDCl_3$) δ 64.3 (C5′), 71.7 (C4′), 74.5 (C3′), 75.5 (C2′), 78.0 (OCH_2N), 103.0 (C5), 104.5 (C1′), 127–135 (aromatic), 143.5 (C6), 150.0 (C=O, C2), 163.5 (C=O, C4), 165.0, 165.3 and 166.0 (C=O, ester); FAB-MS m/z: 609 [M^+ + Na]; Anal calcd for $C_{31}H_{26}O_{10}N_2$:C, 63.48; H, 4.47; N, 4.78 Found: C, 63.37; H, 4.36; N, 4.67.

1-[(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyloxy)methyl]thymine (6b). Prepared according to method B (2.22 mmol) by reacting **4** (1.0 g, 1.87 mmol) and **5b** (0.6 g, 2.22 mmol) in $CHCl_3$ (40 mL) at reflux for 4 h to isoltate the title compound as a white crystalline solid (0.88 g, 78.6% yield). mp 82-84°C; $[\alpha]_D$ 41.0 (c 1.0, $CHCl_3$); UV λ_{max} (MeOH) nm: 266; IR (KBr) ν_{max} 3176, 2970, 1721, 1684, 1369, 1307, 1269, 1092, 1062 and 1031 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$) δ 1.90 (3H, s, CH_3), 4.50 (1H, dd, *J* = 14.0, 6.5 Hz, H5′), 4.60–4.80 (2H, m, H4′,H5″), 5.10,5.36 (2H, AB type quartet, *J* = 10.0 Hz, OCH_2N), 5.50 (1H, s, H1′), 5.70 (1H, d, *J* = 5.0 Hz, H2′), 5.80 (1H, dd, *J* = 4.0 Hz, H3′), 6.98 (1H, s, H6), 7.20–8.20 (15H, m, aromatic), 8.50 (1H, br s, NH); ^{13}C NMR (50 MHz; $CDCl_3$) δ 12.2 (CH_3), 64.6 (C5′), 74.5 (C4′), 76.0 (C3′), 78.0 (C2′), 80.0 (OCH_2N), 104.7 (C1′), 111.5 (C5), 127–135 (aromatic), 151.0 (C=O,C2) 164.0 (C=O,C4) 164.8, 165.0 and 165.8 (C=O,ester); FAB-MS m/z: 601 [M^+ + H]; Anal. cacld for $C_{32}H_{28}O_{18}N_2$:C, 63.99; H, 4.70; N, 4.66. Found: C, 64.17; H, 4.62; N, 4.59.

1-[(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyloxy)methyl]cytosine (6c). Prepared according to method A (6.74 mmol) by reacting **4** (3.0 g, 5.61 mmol) and **5a** (1.71 g, 6.74 mmol) in $CHCl_3$ (30 mL) at room temperature for 6 h to isolate after chromatographic separation (ethyl acetate:chloroform, 2:1) **7c** (1.47 g, 47.4% yield)) as a crystalline solid mp 180–82°C (lit.[13] mp 182–83°C) and the title compound **6c** (0.96 g, 29.5% yield) as a white crystalline solid. mp 178–181°C; $[\alpha]_D$ 29.0 (c 1.0, $CHCl_3$); UV λ_{max} (MeOH) nm: 271; IR (KBr) ν_{max} 3336, 3200, 1728, 1664, 1616, 1488, 1370, 1264, 1088 and 1040 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$) δ 4.50 (1H, dd, *J* = 13.0, *J* = 5.0 Hz, H5′), 4.60–4.80 (2H, m, H4′,H5″), 5.15, 5.40 (2H, AB type quartet, *J* = 10.0 Hz, OCH_2N), 5.60 (1H, s, H1′), 5.70 (d, *J* = 5.0 Hz, H2′), 5.85 (1H,dd, *J* = 3.0 Hz, H3′), 5.95 (1H,d, *J* = 7.5 Hz, H5), 7.15–8.15 (16H, m, H6, aromatic); ^{13}C NMR (50 MHz; $CDCl_3$) δ 64.7 (C5′), 72.1 (C4′), 75.5 (C2′), 76.5 (C3′), 79.5 (OCH_2N), 104.2 (C1′), 128–135 (aromatic), 144.6 (C6), 156.1 (C4), 165.1 (C=O,C2) 165.4, 166.0, 166.1 (C=O,ester); FAB-MS m/z: 586 [M^+ + H]; Anal. cald for $C_{31}H_{27}O_9N_3$: C, 63.58; H, 4.65; N, 7.18. Found: C, 63.41; H, 4.59; N, 7.12.

***N*[4]Benzoyl-1-[(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyloxy)methyl]cytosine (6d).** Prepared according to method B (1.11 mmol) by reacting **4** (0.5 g, 0.93 mmol) and **5d** (0.4 g, 1.11 mmol) in $CHCl_3$ (20 mL) at reflux temperature for 4 h to isoltate after

chromatographic separation (ethylacetate:chloroform, 2:1) **7d** (0.1 g, 17.0% yield) as a crystalline solid mp 205–7°C (lit.[13] mp 206.5–208°C) and the title compound **6d** (0.33 g, 52.0% yield) as a white crystalline solid. mp 126–128°C; $[\alpha]_D$ 9.0 (c 1.0, $CHCl_3$); UV λ_{max} (MeCN) nm: 258; IR (KBr) ν_{max} 3062, 2915, 1723, 1662, 1604, 1530, 1454, 1307, 1270, 1100, 1046, 970, 815 and 692 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$) δ 4.50 (1H, dd, *J* = 13.0, 5.0 Hz, H5′), 4.55–4.75 (2H, m, H4′,H5″), 5.20, 5.50 (2H, AB type quartet, *J* = 10.0 Hz, OCH_2N), 5.60 (1H, s, H1′), 5.65 (1H, d, *J* = 5.0 Hz, H2′), 5.70–5.90 (1H, m, H3′), 7.20–8.15 (17H, m, H5,H6,aromatic); FAB-MS m/z: 690 $[M^+ + H]$; Anal. calcd for $C_{38}H_{31}O_{10}N_3$:C, 66.18; H, 4.53; N, 6.09. Found: C, 66.31; H, 4.48; N, 6.02.

***N*^{6}-Benzoyl-9-[(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyloxy)methyl]adenine (6e).** Prepared according to method B (3.7 mmol) by reacting **4** (1.0 g, 1.87mmol) and **5a** (0.86 g, 2.24 mmol) in MeCN (40 mL) at room temperature for 16 h to isoltate after chromatographic separation (ethyl acetate:chloroform, 2:1) **7e** (0.44 g, 34.9% yield)) as a crystalline solid mp 89–91°C (lit.[13] mp 88–92°C) and the title compound **6e** (0.6 g, 45.4% yield) as a yellowish solid. mp 113–116°C; $[\alpha]_D$ 7.0 (c 1, $CHCl_3$); UV λ_{max} (MeCN) nm: 277; IR (KBr) ν_{max} 3323, 3085, 1723, 1616, 1508, 1446, 1323, 1261, 1062, 1015 and 708 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$) δ 4.50 (1H, dd, *J* = 14.0, 5.0 Hz, H5′), 4.65–4.90 (2H, m, H4′,H5″), 5.50 (1H, s, H1′), 5.60–6.00 (4H, m, OCH_2N,H2′,H3′), 7.20–8.20 (21H, m, H8, aromatic), 8.80 (1H,s, H2), 9.00 (1H, br s, NH); ^{13}C NMR (50 MHz; $CDCl_3$) δ 45.2 (C5′), 64.3 (C4′), 75.3 (C2′), 81.1 (OCH_2N), 104.0 (C1′), 122.1 (C5),125–135 (aromatic) 143.0 (C8), 149.7 (C4), 152.0 (C2), 153.1 (C6), 164.8, 165.0, 165.3, 166.0 (C=O,ester); FAB-MS m/z: 714 $[M^+ + H]$; Anal. cacld for $C_{39}H_{31}O_9N_5$:C, 65.68; H, 4.37; N, 9.82. Found: C, 63.81; H, 4.21; N, 9.72.

***N*^{2}-Acetyl-9-[(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyloxy)methyl]guanine (6f) *N*^{2}-Acetyl-7-[(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyloxy)methyl]guanine (6g).** Prepared according to method B (2.24 mmol) by reacting **4** (1.0 g, 1.87 mmol) and **5f** (0.91 g, 2.24 mmol) in 1,2-dichloroethane (40 mL) at reflux temperature for 2 h to isoltate after chromatographic separation (ethyl acetate:chloroform, 3:1) the title compound **6f** (0.38 g, 29.7% yield) as a white crystalline solid. mp 125–127°C; $[\alpha]_D$ 42.0 (c 1, $CHCl_3$); UV λ_{max} (MeCN) nm: 281; IR (KBr) ν_{max} 3170, 3046, 2923, 1730, 1677, 1600, 1554, 1430, 1338, 1261, 1077, 1000 and 692 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$) δ 2.38 (3H, s, Ac), 4.60–4.85 (3H,m, H4′,H5′,H5″), 5.50 (1H,s, H1′), 5.45–5.65 (2H, AB type quartet, *J* = 10.0 Hz, OCH_2N), 5.60–5.80 (2H, m, H2′,H3′), 7.15–8.00 (15H, m, aromatic), 10.42 (1H, br s, NH), 12.00 (1H, br s, NH); FAB-MS m/z: 668 $[M^+ + H]$; Anal. cacld for $C_{34}H_{29}O_{10}N_5$:C, 61.16; H, 4.38; N, 10.4. Found: C, 61.28; H, 4.27; N, 10.32.; followed by (**6g**) (0.34 g, 27% yield) as a white crystalline solid. mp 225–228°C; $[\alpha]_D$ − 30.0 (c 1, $CHCl_3$); UV λ_{max} (MeCN) nm: 266; IR (KBr) ν_{max} 3300, 2930, 2861, 1715, 1685, 1616, 1385, 1315, 1261, 1092, 1046, 1030 and 692 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$) δ 2.20 (3H, s, Ac), 4.20–4.80 (3H, m, H4′,H5′,H5″), 5.65 (1H, s, H1′), 5.70–6.08 (4H, m, OCH_2N, H2′,H3′), 7.20–8.20 (15H, m, aromatic), 11.50 (1H, br s, NH), 12.20 (1H,br s, NH); FAB-MS m/z: 668 $[M^+ + H]$; Anal cacld for $C_{34}H_{29}O_{10}N_5$:C, 66.16; H, 4.38; N, 10.49. Found: C, 66.01; H, 4.29; N, 10.33.

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1-[(β-D-Ribofuranosyloxy)methyl]uracil (8a). To a solution of **6a** (0.9g, 1.53 mmol) in methanol (18 mL) was added a catalytic amount of $NaHCO_3$ (0.1 g) and refluxed for 3 h. After completion of the reaction the reaction mixture was neutralized with IR 120 H^+ resin, filtered, washed with methanol (10 mL) and filtrate was evaporated to a residue. The residue was dissolved in water (25 mL) washed with chloroform (25 mL), the water phase was concentrated to isolate the title compound as a white solid in 93% yield (0.39 g), mp 113–115°C; $[\alpha]_D$ 144.0 (c 1.0, H_2O); UV λ_{max} (H_2O) nm: 260, (0.1N, NaOH) 261; IR (KBr) ν_{max} 3370, 3046, 2830, 2315, 1685, 1446, 1262, 1054, 953 and 815 cm^{-1}; ^1H NMR (400 MHz; D_2O) δ 3.60 (1H, dd, *J* = 10.0,5.5 Hz, H5′), 3.80 (1H, dd, *J* = 4.0 Hz, H5″), 4.05 (1H, m, H3′), 4.12 (1H, d, *J* = 5.5 Hz, H2′), 5.22 (1H, s, H1′), 5.27, 5.40 (2H, AB type quartet, *J* = 11.0 Hz, OCH_2N), 5.90 (1H, d, *J* = 5.5 Hz, H5), 7.80 (1H, d, H6); ^{13}C NMR (50 MHz; D_2O) δ 63.0 (C5′), 71.0 (C4′), 75.0 (C3′), 75.5 (C2′), 83.5 (OCH_2N), 102.5 (C5), 106.0 (C1′), 146.5 (C6), 152.25 (C=O,C2), 166.5 (C=O,C4); FAB-MS m/z: 275 [M^+ + H]; Anal. calcd for $C_{10}H_{14}O_7N_7$:C, 43.80; H, 5.15; N, 10.22. Found: C, 43.67; H, 5.11; N, 10.25.

1-[(β-D-Ribofuranosyloxy)methyl]thymine (8b). To a solution of **6b** (0.7g, 1.16 mmol) in methanol (14 mL) was added a catalytic amount of $NaHCO_3$ (0.08 g) and refluxed for 3 h. to isolate by the work up described for **8a** the title compound as a white crystalline solid in 98.5% yield (0.33 g). mp 188–190°C; $[\alpha]_D$ −22.0 (c 1.0, MeOH); UV λ_{max} (MeOH) nm: 265, (0.1N NaOH) 266; IR (Neat) ν_{max} 3400, 2953, 1693, 1677, 1362, 1330, 1260, 1076 and 1030 cm^{-1}; ^1H NMR (200 MHz; D_2O) δ 1.90 (3H, s, CH_3), 3.60 (1H, dd, *J* = 14.0, 6.5 Hz, H5′), 3.80 (1H, dd, *J* = 4.0 Hz, H5″), 3.90–4.30 (2H, m, H3′,H4′), 5.20 (1H, s, H1′), 5.25, 5.35 (2H, AB type quartet, *J* = 10.0 Hz, OCH_2N), 7.60 (1H, s, H6), 8.00 (1H, br s, NH); ^{13}C NMR (50 MHz; D_2O) δ 10.7 (CH_3), 62.2 (C5′), 70.1 (C4′), 74.0 (C3′), 74.4 (C2′), 82.6 (OCH_2N), 105.2 (C1′), 110.6 (C5), 141.3 (C6), 151.5 (C=O,C2), 166.1 (C=O,C4); FAB-MS m/z: 311 [M^+ + Na]; Anal calcd for $C_{11}H_{16}O_7N_2$:C, 45.83, H, 5.60, N, 9.2. Found: C, 45.91; H, 5.52; N, 9.13.

1-[(β-D-Ribofuranosyloxy)methyl]cytosine (8c). To a solution of **6c** (0.9g, 1.5 mmol) in methanol (18 mL) was added a catalytic amount of $NaHCO_3$ (0.1 g) and refluxed for 3 h. to isolate by the work up described for **8a** the title compound as a white crystalline solid in 75 % yield (0.31 g) as a white solid. mp 146°C; $[\alpha]_D$ 16.0 (c 1, MeOH); UV λ_{max} (MeOH) nm: 268, (0.1N NaOH) 270; IR (Neat) ν_{max} 3446, 1662, 1500, 1384, 1200 and 731 cm^{-1}; ^1H NMR (200 MHz; D_2O) δ 3.60 (1H,dd, *J* = 13.0, 5.0 Hz, H5′), 3.80 (1H,dd, *J* = 3.0 Hz, H5″), 3.90–4.30 (3H, m, H2′,H3′,H4′), 5.20 (1H, s, H1′), 5.20, 5.40 (1H, AB type quartet, *J* = 10.0 Hz,OCH_2N), 6.15 (1H,d, *J* = 7.5 Hz, H5), 7.70 (1H,d, H6); ^{13}C NMR (50 MHz; D_2O) δ 62.1 (C5′), 70.1 (C4′), 74.0 (C3′), 76.0 (C2′), 82.5 (OCH_2N), 105.2 (C1′), 146.0 (C6), 156.6 (C4), 165.5 (C=O,C2); FAB-MS m/z: 274 [M^+ + H]; Anal. calcd for $C_{10}H_{15}O_6N_2$:C, 43.95; H, 5.53; N, 15.38. Found: C, 43.81; H, 5.45; N, 15.22.

9-[(β-D-Ribofuranosyloxy)methyl]adenine (8e). To a solution of **6e** (0.4g, 0.56 mmol) in methanol (8 mL) was added a catalytic amount of $NaHCO_3$ (0.05 g) and refluxed for 5 h. to isolate by the work up described for **8a** the title compound as a white crystalline solid in 83.2% yield (0.14 g). mp 155–158°C; $[\alpha]_D$ − 34.0 (c 1, DMSO); UV λ_{max} (H_2O) nm: 259; IR ?KBr) ν_{max} 3308, 1670, 1685, 1600, 140.8, 1370,

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1285, 1123, 1062, 1023, 962, 800 and 722 cm^{-1}; ^1H NMR (200 MHz;DMSO-d_6) δ 3.20–4.00 (6H,m, H2′,H3′,H4′,H5′,H5″,OH), 4.75 (1H, br s, OH), 4.90 (1H, s, H1′), 5.10 (1H, br s, OH), 5.55, 5.70 (2H,AB type quartet, J = 10.0 Hz, OCH_2N)), 7.25 (2H, br s, NH_2), 8.20 (1H, s, H8), 8.25 (1H,s, H2); ^{13}C NMR (50 MHz; DMSO-d_6) δ 62.6(C5′), 68.6(C4′), 70.6(C3′), 74.5 (C2′), 84.1 (OCH_2N), 105.1 (C1′), 118.6 (C5), 141.5 (C8), 149.6 (C4), 153.0 (C2), 156.0 (C6); FAB-MS m/z: 298 [M^+ + H]; Anal. calcd for $C_{11}H_{15}O_5N_5$:C, 44.44; H, 5.09; N, 23.56. Found: C, 44.51; H, 5.01; N, 23.44.

9-[(β-D-Ribofuranosyloxy)methyl]guanine (8f). To a solution of **6f** (0.3g, 0.44 mmol) in methanol (6 mL) was added a catalytic amount of $NaHCO_3$ (0.05 g) and refluxed for 3 h. to isolate by the work up described for **8a** the title compound as a white crystalline solid in 78.5% yield (0.11 g). mp 260–262°C; $[\alpha]_D$ −4.0 (c 0.5, DMSO); UV λ_{max} (H_2O) nm: 252; IR (KBr) ν_{max} 3353, 3200, 2970, 2892, 2762, 1692, 1646, 1600, 1523, 1477, 1168, 1015, 984, 790, 692 and 570 cm^{-1}; ^1H NMR (300 MHz; DMSO-d_6) δ 3.25–3.60 (2H, m, H5′, H5″), 3.64 (1H, s, H2′), 3.65–4.00 (2H, m, H3′,H4′), 4.65 (1H, s, OH), 4.88 (1H, s, OH), 4.90 (1H, s, H1′), 5.14 (1H, s, OH), 5.35, 5.45 (2H, AB type quartet, J = 10.0 Hz, OCH_2N), 6.55 (2H, br s, NH_2), 7.75 (1H, s, H8), 10.70 (1H, br s, NH); ^{13}C NMR (50 MHz; DMSO-d_6) δ 62.5 (C5′), 68.1 (C4′), 70.5 (C3′), 74.3 (C2′), 84.0 (OCH_2N), 104.7 (C1′), 116.4 (C5), 137.7 (C8), 151.2 (C4), 153.9 (C2), 156.7 (C6); FAB-MS m/z: 314 [M^+ + H]; Anal. calcd for $C_{11}H_{15}O_6N_5$:C, 42.17; H, 4.83; N, 22.36. Found: C, 42.26; H, 4.72; N, 22.2.

7-[(β-D-Ribofuranosyloxy)methyl]guanine (8g). To a solution of **6g** (0.3g, 0.44 mmol) in methanol (6 mL) was added a catalytic amount of $NaHCO_3$ (0.05 g) and refluxed for 5 h. to isolate by the work up procedure described for **8a** the title compound as a white crystalline solid in 93% yield (0.13 g). mp 264°C (decomposed); $[\alpha]_D$ 24.0 (c 0.5, DMSO); UV λ_{max} (H_2O) nm: 285; IR (KBr) ν_{max} 3315, 3154, 2915, 1661, 1538, 1454, 1370, 1210, 1092 and 1030 cm^{-1}; ^1H NMR (500 MHz; DMSO-d_6) δ 3.20–3.60 (2H, m, H5′,H5″), 3.70 (1H, s, H2′), 3.75–3.95 (2H, m, H3′,H4′), 4.60 (1H, s, OH), 4.80 (1H, s, OH), 4.90 (1H, s, H1′), 5.00 (1H, s, OH), 5.60, 5.65 (2H, AB type quartet, J = 10.0 Hz, OCH_2N), 6.20 (2H, br s, NH_2), 8.00 (1H, s, H8), 10.90 (1H, br s, NH); ^{13}C NMR (75 MHz; DMSO-d_6) δ 63.4 (C5′), 71.4 (C4′), 72.3 (C3′), 75.3 (C2′), 84.8 (OCH_2N), 105.7 (C1′), 106.4 (C5), 145.0 (C8), 154.0 (C2), 155.3 (C6), 161.0 (C4); FAB-MS m/z: 314 [M^+ + H]; Anal. calcd for $C_{11}H_{15}O_6N_5$:C, 42.17; H, 4.83; N, 22.36. Found: C, 42.24; H, 4.71; N, 22.19.

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